Oral-gut axis in systemic disease: A barrier-metabolism-immunity three-dimensional regulatory model (Review)

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Received March 9, 2026; Accepted June 9, 2026

DOI: 10.3892/ijmm.2026.5907

Abstract. The oral-gut axis is an interorgan regulatory network connecting the two core microbial niches in the human body. It sustains systemic homeostasis through bidirectional microbial translocation, metabolite signaling and immune crosstalk. The present review presented a novel barrier-metabolism-immunity three-dimensional regulatory framework that clarifies the core mechanisms of oral-gut axis dysregulation: Bidirectional translocation of oral and gut microbiota disrupts microbial homeostasis; key metabolites, including short-chain fatty acids and trimethylamine N-oxide, mediate interorgan signaling; immune cell migration and barrier damage collectively constitute the pathological basis, which drives multisystem disorders through secondary axes. The present study classified oral-gut axis imbalance into three quantifiable subtypes: Barrier-dominant, metabolism-dominant and immunity-dominant, each linked to distinct diseases such as inflammatory bowel disease, type 2 diabetes mellitus and rheumatoid arthritis. Accordingly, a stratified, personalized intervention strategy was proposed. Current challenges include difficulties in causal verification, substantial interindividual variability in intervention efficacy and limited tools for real-time interorgan tracking. Future research will benefit from microbiota gene editing, multi-omics integration and in vivo imaging to advance mechanistic understanding and clinical translation. This three-dimensional model provides a standardized theoretical foundation and practical guidance for the diagnosis and treatment of oral-gut axis-related diseases.

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Key words: oral-gut axis, microbiota dysbiosis, microbial translocation, metabolite signaling, immune crosstalk

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1. Introduction

The oral cavity and gut represent the body's two core microbial habitats, hosting distinct and diverse communities shaped by diet, hygiene, age and lifestyle, with high interindividual variability and site-specific differences, while gut microbiota exhibits dynamic plasticity (1). Oral microbiota maintains mucosal integrity, regulates immunity and inhibits pathogens, whereas gut microbiota supports digestion, nutrient absorption and immune homeostasis; short-chain fatty acids (SCFAs) produced by microbial fiber fermentation supply energy to intestinal epithelial cells, modulate mucosal immunity and preserve barrier function (2). Comparative analyses of non-human primates further reveal that evolutionary conservation of the oral microbiome and age-related shifts in gut microbial diversity are associated with chronic diseases in older adults (3). As research advanced, the oral-gut axis concept expanded from unidirectional oral-to-gut microbial colonization, exemplified by increased intestinal *Porphyromonas gingivalis* in periodontitis patients correlating with inflammatory bowel disease (IBD) activity (4,5), to a bidirectional network involving microbial translocation, immune crosstalk, metabolic signaling, neural and humoral communication (6). Yet the high comorbidity of periodontitis and rheumatoid arthritis (RA), plus inconsistent responses of joint inflammation to periodontal therapy (7,8), reveals uncharacterized regulatory nodes in the axis. The conventional linear microbiota-metabolism-immunity model cannot explain such clinical heterogeneity, prompting two key questions: Why do identical oral interventions produce divergent outcomes and what are the central regulatory nodes

driving axis-related pathogenesis? To address these gaps, the barrier-metabolism-immunity three-dimensional regulatory network was developed as a unifying framework.

The existing linear microbiota-metabolism-immunity model has three inherent limitations that make it impossible to fully explain the regulatory mechanism of the oral-gut axis: First, it only emphasizes the one-way conduction relationship (microbiota-metabolism-immunity) and ignores the dynamic cyclic interaction between the three (6,9); second, it regards the barrier function as a pathological result of dysbiosis rather than a core initiating regulatory node, failing to capture the root cause of axis imbalance (10); third, it only focuses on correlation analysis between microbiota and diseases, without stratifying the causal relationship between microbiota-driven disease and disease-driven microbiota dysbiosis, thus unable to explain the clinical heterogeneity of intervention efficacy (11). These limitations lead to the lack of a unified theoretical framework for the study of the oral-gut axis and also make clinical intervention lack clear targeted guidance.

To address the aforementioned scientific questions, The present review proposes a 'barrier-metabolism-immunity three-dimensional regulatory network' model (Fig. 1), clarifying the core functions and interactive relationships of each link.

Barrier layer. The oral/gut barrier serves as the first gate, and its integrity directly determines the efficiency of microbial translocation. Experiments have confirmed that the expression level of intestinal tight junction protein zonula occludens-1 (ZO-1) is negatively associated with the intestinal colonization ability of *Porphyromonas gingivalis*. Infection with this bacterium can markedly reduce ZO-1 expression, thereby enhancing its colonization efficiency in the gut and exacerbating gut microbiota dysbiosis (12,13). This finding highlights the fundamental role of barrier function in axis homeostasis and provides direct evidence for barrier repair-based intervention strategies.

Metabolism layer. Metabolites act as signal amplifiers and exhibit specific concentration threshold effects in different diseases. For example, the fecal butyrate concentration in healthy individuals is mostly 10-30 μmol/g (14); in IBD patients, it often decreases markedly to 5-15 μmol/g (15); the median fecal butyrate concentration in type 2 diabetes mellitus (T2DM) patients, especially those with type 1 diabetes mellitus (T1DM), is ~7.8 μmol/g (16); a trimethylamine N-oxide (TMAO) level >10 μmol/l indicates an increased cardiovascular risk (17); each 5 μmol/l increase in TMAO concentration is associated with a 9% higher risk of hypertension and each 10 μmol/l increase with a 20% higher risk (18). The concentration-dependent effect of metabolites suggests that precise regulation of metabolite levels may become a key entry point for disease intervention.

Immunity layer. The immune system serves as the 'executive terminal' in host defense and the immune response of the oral mucosa, as the first barrier of the upper digestive tract exposed to exogenous microorganisms, plays an important regulatory role. Upon antigen stimulation, T cells in the oral mucosa upregulate the gut-homing receptor CC chemokine receptor 9 (CCR9) and chemokine receptor CXCR3 with the assistance of local dendritic cells, enabling them to migrate to the small intestine (10). These receptors can specifically recognize CCL25 (CCR9 ligand) and CXCL9/10/11 (CXCR3 ligands) secreted by small intestinal epithelial cells, thereby driving oral-derived effector T cells or regulatory T cells (Tregs) to enter the intestinal mucosa (19). The interorgan migration characteristics of immune cells reveal a direct pathway for oral-gut immune crosstalk, providing new ideas for immune-targeted interventions.

Compared with the traditional linear model, the three-dimensional barrier-metabolism-immunity model features three key innovations: It identifies barrier function as the initiating regulatory node governing microbial translocation and signal transmission, reveals dynamic reciprocal interactions among barrier, metabolism and immunity and establishes causal stratification and subtype classification to shift studies from correlation analysis to causal intervention and from single-target to stratified combined therapy, thereby filling theoretical gaps in oral-gut axis regulation. Oral-gut axis dysbiosis is critically implicated in chronic inflammatory diseases, metabolic disorders and tumors (20-22); for example, patients with IBD and periodontitis exhibit reduced oral and gut microbial α-diversity, elevated *Proteobacteria*, increased proinflammatory cytokines and impaired barrier function, creating a self-reinforcing vicious cycle (23), while population heterogeneity, such as higher *Bacteroidetes* abundance in Asian gut microbiota, may alter responses to oral interventions in T2DM patients (10). Nonetheless, major limitations remain, including incompletely defined molecular mechanisms and insufficient large-scale clinical validation of interventions (24). The present review centered on metabolite-immune crosstalk and systematically summarized three modules: Core mechanisms of interorgan signal communication and immune regulation, disease associations linking axis dysregulation to systemic disorders via multi-omics and clinical evidence and clinical translation covering biomarker development, targeted therapy, nanodelivery systems and systemic benefits of oral health care.

2. Core mechanisms of the oral-gut axis

Under homeostatic conditions, the axis maintains stability via five hierarchical mechanisms. During dysregulation, a pathological cascade proceeds as: Barrier damage-microbial translocation-metabolic disturbance-immune dysregulation-secondary axis activation (25). This integrated cascade reflects the sequential and circular interplay among structural, microbial, metabolic and immune events that underpin systemic diseases, which has been systematically verified by studies on dietary intervention, microbial regulation and inflammatory response (Fig. 2).

Bidirectional microbial translocation. Bidirectional microbial translocation between the oral cavity and gut represents the initiating event of oral-gut axis dysregulation; oral pathobionts can reach the intestine via deglutition or hematogenous routes, while gut dysbiosis retrogradely modulates oral microbiota through metabolic and immune signals to form a mutual regulatory loop and this bidirectional crosstalk constitutes

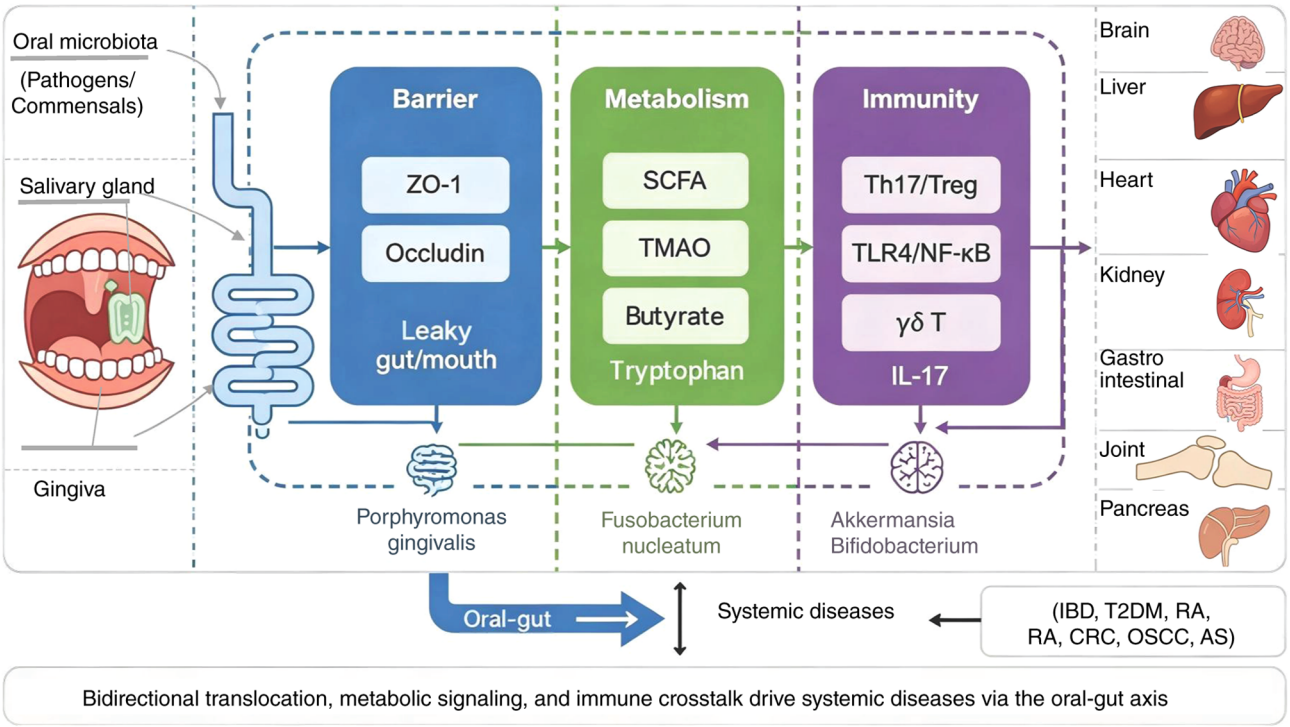

Figure 1. The oral-gut axis in systemic diseases: a barrier-metabolism-immunity three-dimensional regulatory model. Schematic overview of the oral-gut axis as a bidirectional interorgan network connecting oral and gut microbiota. Under homeostatic conditions, barrier integrity, balanced metabolite signaling (SCFAs, tryptophan metabolites, TMAO) and coordinated immune crosstalk maintain systemic stability. During dysregulation, pathogenic oral bacteria translocate to the intestine, disrupt tight junctions, alter metabolite profiles and trigger abnormal immune responses. These events collectively drive the pathogenesis of multiple systemic diseases via barrier-metabolism-immunity crosstalk. Key pathogens include *Porphyromonas gingivalis* and *Fusobacterium nucleatum*; key protective taxa include *Akkermansia* and *Bifidobacterium*. SCFAs, short-chain fatty acids; TMAO, trimethylamine N-oxide; ZO-1, zonula occludens-1; Occludin, occludin tight junction protein; Th17, T helper 17 cell; Treg, regulatory T cell; TLR4, toll-like receptor 4; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; γδ T, gamma delta T lymphocyte; IL-17, interleukin 17; IBD, inflammatory bowel disease; T2DM, type 2 diabetes mellitus; RA, rheumatoid arthritis; CRC, colorectal cancer; OSCC, oral squamous cell carcinoma; AS, ankylosing spondylitis. The schematic outline of the image was created using Doubao AI (ByteDance).

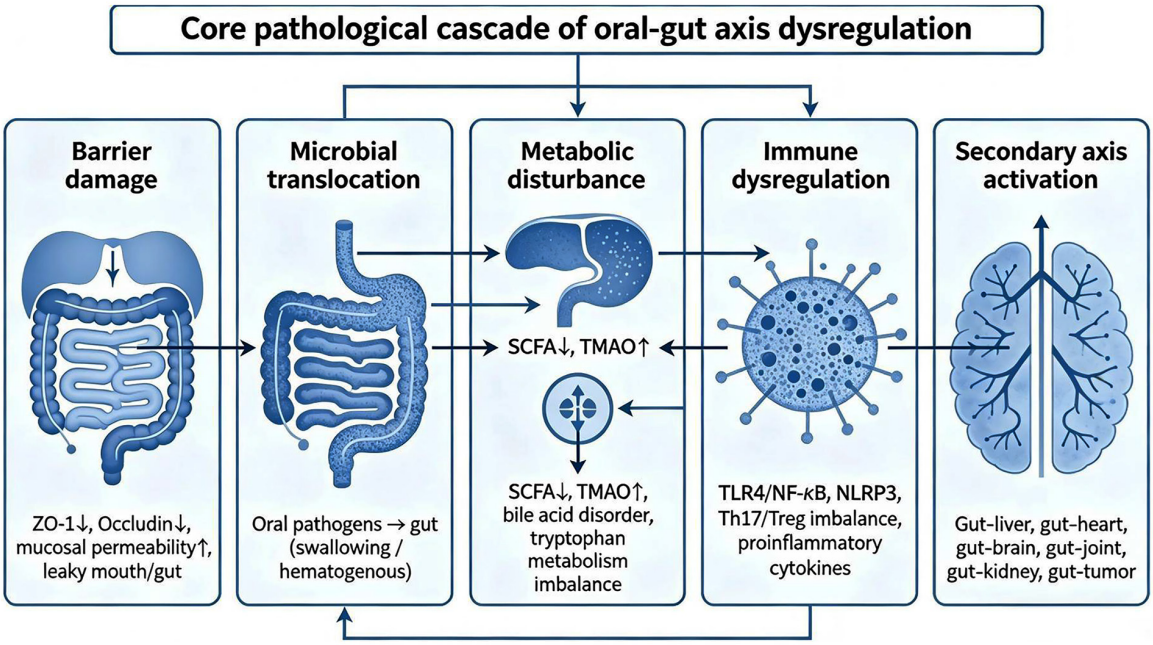

Figure 2. Core pathological cascade of oral-gut axis dysregulation. The stepwise pathological cascade underlying oral-gut axis dysfunction. Barrier damage: impaired oral and intestinal epithelial integrity with downregulated tight junction proteins (ZO-1, occludin). Microbial translocation: oral pathogenic bacteria colonize the gut via deglutition and hematogenous routes. Metabolic disturbance: reduced SCFA production, elevated TMAO and disordered bile acid and tryptophan metabolism. Immune dysregulation: activated TLR4/NF-κB signaling, imbalanced Th17/Treg ratio and enhanced proinflammatory cytokine release. Secondary axis activation: signals propagate to distant organs via gut-liver, gut-heart, gut-brain, gut-joint and gut-kidney axes, leading to multisystem disorders. ZO-1, zonula occludens-1; SCFA, short-chain fatty acid; TMAO, trimethylamine N-oxide; TLR4, Toll-like receptor 4; NF-κB, nuclear factor-κB; Th17, T helper 17 cell; Treg, regulatory T cell. The schematic outline of the image was created using Doubao AI (ByteDance).

functional interaction rather than simple microbial migration, reshaping the microecological structure of both sites. Oral pathogens including *Porphyromonas gingivalis* and *Fusobacterium nucleatum* translocate to the gut, disrupt intestinal ecological stability and promote intestinal inflammation and tumor progression (26,27). *Fusobacterium nucleatum* can colonize the colon, activate the nuclear factor-κB (NF-κB) pathway, upregulate CCL22 expression and recruit Tregs to foster an immunosuppressive tumor microenvironment that facilitates colorectal cancer (CRC) development (26). Conversely, gut dysbiosis in metabolic disorders such as T2DM impairs oral mucosal immunity, reduces beneficial oral bacteria and increases susceptibility to periodontitis (28). Translocation represents functional cross-talk that initiates systemic pathological cascades and coordinated regulation of oral and gut microbiota achieves improved therapeutic effects than single-site intervention, as shown by the improved alleviation of comorbid IBD and periodontitis through simultaneous oral-gut microbial regulation.

Interorgan metabolic signal disturbance. Microbial metabolites including SCFAs, bile acids, tryptophan derivatives such as indole-3-acetic acid (IAA) and TMAO act as critical interorgan signaling molecules and their dysregulation directly contributes to metabolic, cardiovascular, inflammatory diseases and tumors as core messengers in oral-gut axis communication (25,27,29). Among these, SCFAs and tryptophan metabolites are the most extensively studied and key to maintaining axis homeostasis (25,29). Reduced SCFA levels, particularly butyrate, impair intestinal epithelial energy supply and barrier function and are closely associated with IBD and metabolic disorders (28,30). Elevated TMAO promotes vascular inflammation and hypertension by activating inflammatory pathways (31). Disturbed tryptophan metabolism lowers IAA levels and exerts tissue-specific bidirectional regulatory effects by either activating the pregnane X receptor-interleukin (IL)-35 pathway to suppress tumors or the aryl hydrocarbon receptor (AhR) pathway to worsen pneumonia (29,32,33). Gut dysbiosis-induced bile acid metabolism disorders disrupt mucosal immune homeostasis and promote intestinal inflammation (34). Metabolic disorders serve as signal amplifiers in axis dysfunction and targeted modulation of metabolite synthesis or action such as SCFA supplementation, TMAO synthesis inhibition, or IAA regulation can effectively interrupt pathological progression, offering a new direction for the clinical treatment of oral-gut axis-related diseases.

Abnormal immune crosstalk. Translocated bacteria and their metabolites activate innate and adaptive immune pathways, with Toll-like receptor 4 (TLR4)/NF-κB, mitogen-activated protein kinase/NF-κB and NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome as core pathways. Oral mucosal T cells upregulate CCR9 and CXCR3 to migrate to the intestine and directly link oral and gut immunity, while T helper 17 (Th17)/Treg imbalance, autoantibody cross-reactivity and γδT cell dysfunction further amplify systemic inflammation to form a systemic immune response network (35-37). Lipopolysaccharide (LPS) derived from oral pathogens activates the TLR4/NF-κB pathway and increases the release of proinflammatory cytokines including IL-1β, IL-6 and tumor necrosis factor-α, a key mechanism by which oral inflammation induces intestinal injury (37,38). Oral immune cells home to the intestinal lamina propria via CCR9/CXCR3 and directly participate in intestinal immune regulation (39). Th17/Treg imbalance caused by SCFA deficiency or reduced tryptophan metabolites aggravates joint inflammation in RA and intestinal inflammation in colitis (28,40). Plant lactobacillin Bio-LP1 inhibits excessive activation of the TLR4 pathway, reduces proinflammatory factors and restores immune balance (35). Immune crosstalk serves as the effector terminal of axis dysfunction; local immune alterations in the oral cavity can remotely regulate intestinal immunity to form an integrated mucosal immune network and targeting immune crosstalk nodes such as TLR4, NF-κB and Th17/Treg balance can effectively block systemic inflammatory spread, representing a key target for treating oral-gut axis-related multi-system diseases.

Barrier dysfunction. Damage to oral and intestinal barriers (such as 'leaky mouth' or 'leaky gut') removes spatial isolation between the microbiota and the host, accelerating microbial translocation and toxin (such as LPS) diffusion as the initiating link of oral-gut axis dysregulation. Tight junction proteins (ZO-1, occludin, claudin-1) and the urinary lactulose/mannitol (L/M) ratio serve as quantitative biomarkers for barrier function, with their expression levels closely related to the severity of axis dysfunction (35-37). Downregulated expression of ZO-1, occludin and claudin-1 increases intestinal permeability, commonly observed in dextran sulfate sodium-induced colitis, LPS-induces intestinal injury and salt stress-induced fish systemic inflammation (36-38). Barrier disruption enables LPS entry into the circulation, activates systemic inflammatory pathways and induces multi-organ injury (31,38). Barrier repair agents such as chitosan oligosaccharides (COS), hydroxyethyl oligosaccharide extract polysaccharide (HOEP) and Bio-LP1 restore tight junction structure, increase mucin 2 expression, reduce mucosal leakage and block the pathological cascade (28,34,35). COS improve intestinal villus morphology, decrease intestinal mucosal permeability and repair the intestinal physical barrier (28). Barrier integrity represents the foundational gatekeeper of axis homeostasis and early barrier repair is the most efficient strategy to block the entire pathological cascade by directly preventing microbial translocation and toxin diffusion to cut off the source of systemic inflammation.

Activation of secondary axes. The oral-gut axis propagates signals to distal organs via secondary axes including gut-liver, gut-lung, gut-brain, gut-joint and gut-kidney axes, expanding local disorders into systemic diseases and these secondary axes rely on metabolite signals, immune crosstalk and neural-humoral regulation to form a multi-organ regulatory network (31,41,42). The gut-joint axis mediates RA progression; Fengshining Decoction enriches butyrate-producing bacteria, raises butyrate levels, inhibits the histone deacetylase/NF-κB pathway, repairs intestinal barrier and alleviates joint inflammation (43). The gut-lung axis relieves acute lung injury through SCFA signals that strengthen intestinal barrier, suppress systemic inflammation and directly protect lung tissue (41). The gut-liver axis is involved in non-alcoholic

Table I. Secondary interorgan axes and associated systemic diseases.

Secondary axis	Target organ/system	Typical diseases
Oral-gut-liver axis	Liver	NAFLD, liver fibrosis
Oral-gut-heart axis	Cardiovascular system	AS, hypertension
Oral-gut-brain axis	Brain	PD, epilepsy
Oral-gut-joint axis	Joint	RA
Oral-gut-kidney axis	Kidney	Diabetic nephropathy
Oral-gut-tumor axis	Gastrointestinal/oral tract	CRC, OSCC

NAFLD, non-alcoholic fatty liver disease; AS, atherosclerosis; PD, Parkinson's disease; RA, rheumatoid arthritis; CRC, colorectal cancer; OSCC, oral squamous cell carcinoma.

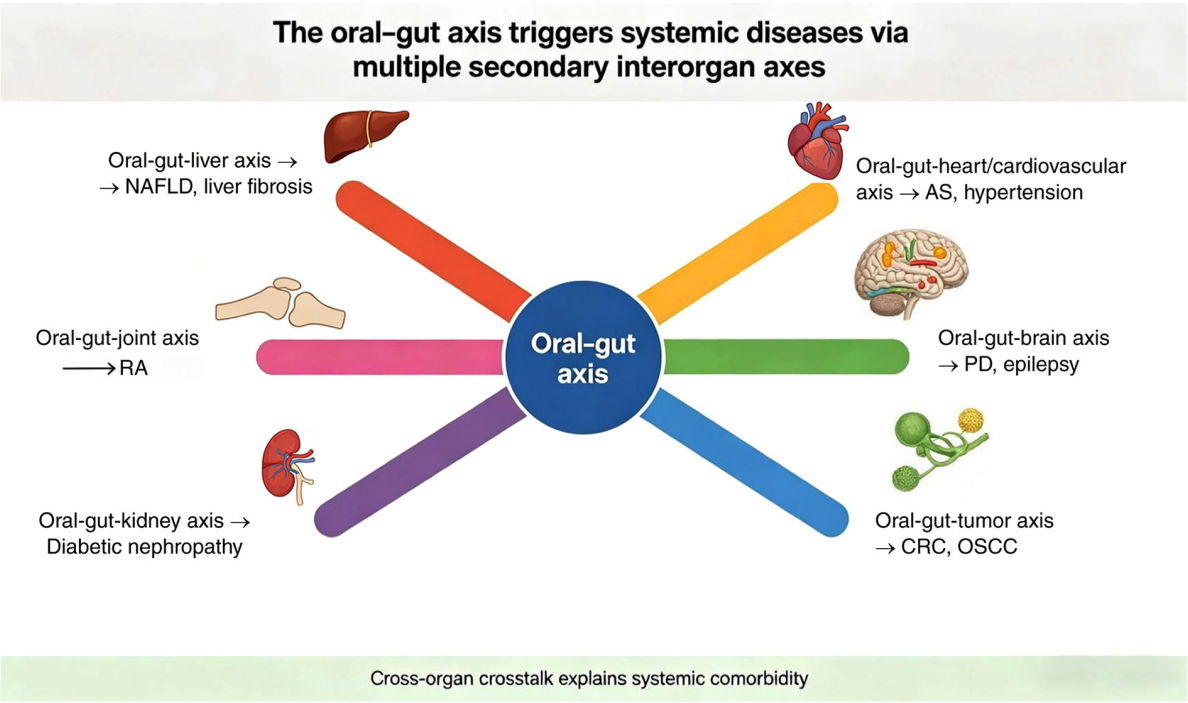

Figure 3. The oral-gut axis propagates systemic disorders via multiple secondary interorgan axes. Schematic illustration showing that the oral-gut axis acts as a central hub that transmits pathogenic signals to distal organs through interconnected secondary axes. Pathological signals originating from oral-gut axis dysregulation (including microbial translocation, metabolic disturbance and immune dysregulation) spread systemically through the oral-gut-liver axis (NAFLD, liver fibrosis), oral-gut-heart/cardiovascular axis (AS, hypertension), oral-gut-brain axis (PD, epilepsy), oral-gut-joint axis (RA), oral-gut-kidney axis (diabetic nephropathy) and oral-gut-tumor axis (CRC, OSCC). This multi-axis cross-talk explains the high comorbidity between periodontal/oral diseases and systemic disorders and highlights the potential of targeting the oral-gut axis for simultaneous multi-organ protection. NAFLD, non-alcoholic fatty liver disease; AS, atherosclerosis; PD, Parkinson's disease; RA, rheumatoid arthritis; CRC, colorectal cancer; OSCC, oral squamous cell carcinoma. The schematic outline of the image was created using Doubao AI (ByteDance).

fatty liver disease (NAFLD) and cholestatic liver injury; intestinal inflammation can inhibit bile acid synthesis via the LPS-NF-κB pathway to mitigate liver damage (42,44). The gut-kidney axis drives diabetic nephropathy; gut dysbiosis-induced SCFA reduction and LPS translocation activate renal inflammatory pathways and worsen fibrosis (31). As shown in Table I, secondary axes account for the multisystem comorbidity of oral-gut axis disorders such as periodontitis complicated with RA, diabetes and chronic kidney disease; targeting the oral-gut axis delivers simultaneous multi-organ benefits that are superior to single-organ intervention and offers a novel strategy for managing complex multi-system diseases (Fig. 3).

Stratification of causal relationships in oral-gut axis imbalance. The imbalance of the oral-gut axis and systemic diseases is not a single causal relationship, but there is a clear three-layer causal model that can effectively distinguish between 'microbiota interaction driven diseases' and 'disease driven microbiota disorders', providing causal basis for the formulation of clinical intervention strategies (Table II).

Oral-driven. Oral flora disorder occurs first; pathogenic bacteria break through the intestinal barrier through translocation, disrupting intestinal microecological stability and oral-gut flora cooperatively drives systemic diseases, such as periodontitis → IBD/RA/atherosclerosis (AS). In this mode, local oral antibacterial and intestinal barrier repair are the

Table II. Causal stratification of oral-gut axis imbalance.

Causal type	Initiating site	Core mechanism	Typical disease paradigm
Oral-driven	Oral cavity	Oral pathogens translocate to gut; barrier disruption initiates dysbiosis	Periodontitis → IBD/RA/AS
Gut-driven	Gut	Gut dysbiosis retrogradely disturbs oral microbiota	T2DM/obesity → periodontitis
Systemically driven	Systemic condition	Systemic disease drives dual oral gut dysbiosis; forms vicious cycle	Obesity + periodontitis; Long COVID

IBD, inflammatory bowel disease; RA, rheumatoid arthritis; AS, atherosclerosis; T2DM, type 2 diabetes mellitus.

Table III. Subclassification of oral-gut axis imbalance: biomarkers and representative diseases.

Subtype	Key biomarkers	Representative systemic diseases
Barrier-dominant	L/M ratio ↑, ZO-1/Occludin ↓, LPS ↑, DAO ↑	IBD, chronic periodontitis, CAP, alcoholic liver injury, Long COVID
Metabolism-dominant	Butyrate ↓, SCFA ↓, TMAO ↑, bile acid disorder	T2DM, hypertension, NAFLD, obesity, AS, epilepsy
Immunity-dominant	IL-17 ↑, Th17/Treg ↑, TLR4/NF-κB ↑, NLRP3 activation	RA, CRC, OSCC, PD, SLE, T1DM, osteoporosis
Overlap subtype	Combined abnormalities of two or three panels	Diabetic periodontitis, periodontitis + AS

L/M, lactulose/mannitol; LPS, lipopolysaccharide; DAO, diamine oxidase; SCFA, short-chain fatty acid; TMAO, trimethylamine N-oxide; IBD, inflammatory bowel disease; CAP, chronic apical periodontitis; T2DM, type 2 diabetes mellitus; NAFLD, non-alcoholic fatty liver disease; AS, atherosclerosis; RA, rheumatoid arthritis; CRC, colorectal cancer; OSCC, oral squamous cell carcinoma; PD, Parkinson's disease; SLE, systemic lupus erythematosus; T1DM, type 1 diabetes mellitus.

core intervention strategies and there is evidence to prove that the intervention effect of synchronously regulating the oral-gut microbiota is markedly improved than that of single intestinal microbiota regulation (45).

Gut-driven. Activation driven by gut microbiota; the gut microbiota is first disrupted and affects the oral microbiota through metabolic/immune signal feedback, leading to an imbalance of the oral microbiota. The synergistic effect of gut-oral microbiota exacerbates disease progression, such as T2DM/obesity → periodontitis, IBD → oral mucosal inflammation. In this mode, gut microbiota remodeling and oral mucosal immune regulation are the core intervention strategies and regulating gut microbiota can markedly improve oral microbiota and disease symptoms (46).

Systemically driven. The two-way driving of systemic diseases; systemic diseases (such as obesity and long COVID) drive the disorder of oral and intestinal flora at the same time. At this time, oral-gut flora is not the initiating factor of the disease, but it will amplify the pathological effect through interaction, forming a vicious circle of disease-flora disorder-disease aggravation. In this mode, on the basis of treating the primary disease, synchronously regulating the core links of the oral-gut axis (barrier + metabolism + immunity) can effectively break the vicious cycle. For example, obesity combined with periodontitis requires synchronous weight loss + oral antibacterial + intestinal metabolism regulation (47).

The aforementioned three causal models are not completely independent and can be transformed into each other during disease progression, with barrier function damage as an important intermediate link. Therefore, barrier repair is the basic intervention strategy in all models.

3. Disease associations organized by dominant subtype

As shown in Table III, diseases are stratified based on the primarily dysregulated dimension, with clear biomarker thresholds for clinical practice and the specific characteristics are supplemented based on the latest research evidence of oral-gut axis imbalance (Fig. 4).

Barrier-dominant diseases. Biomarker criteria: Elevated urinary L/M ratio, reduced ZO-1/occludin, increased mucosal permeability, elevated LPS and diamine oxidase levels, decreased tight junction protein expression (ZO-1, occludin, claudin).

IBD. IBD is marked by oral pathogenic bacterial translocation, impaired intestinal mechanical barrier and downregulated tight junction proteins. Oral *Fusobacterium nucleatum* (Fn) colonizes the injured

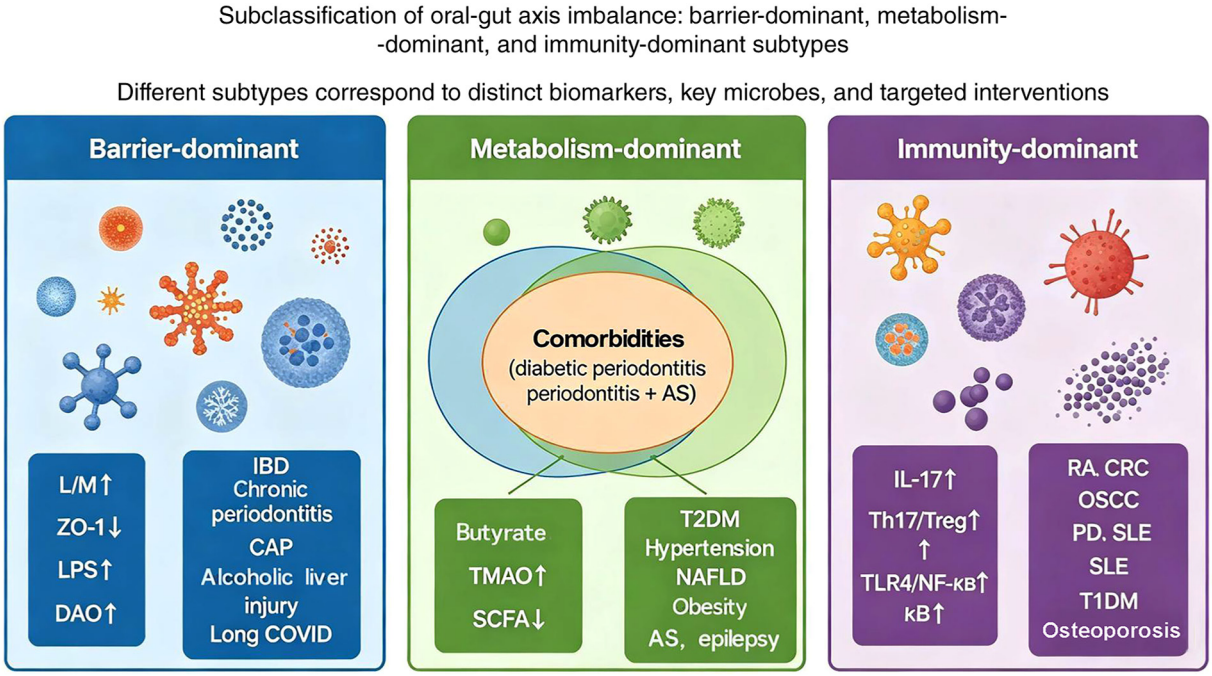

Figure 4. Subclassification of oral-gut axis imbalance into three quantifiable subtypes. Stratification of oral-gut axis-related diseases based on the dominant dysregulated module. Barrier-dominant subtype is characterized by elevated intestinal permeability, reduced tight junction proteins and increased LPS levels, exemplified by IBD, chronic periodontitis, CAP, alcoholic liver injury and Long COVID. Metabolism-dominant subtype features reduced SCFAs, elevated TMAO and disordered energy metabolism, including T2DM, hypertension, NAFLD, obesity, AS and epilepsy. Immunity-dominant subtype shows elevated IL-17, imbalanced Th17/Treg and activated inflammatory signaling, including RA, CRC, OSCC, PD, SLE-hypertension, T1DM and osteoporosis. Overlap subtypes exhibit combined abnormalities and occur in complex comorbidities. LPS, lipopolysaccharide; IBD, inflammatory bowel disease; CAP, chronic apical periodontitis; SCFA, short-chain fatty acid; TMAO, trimethylamine N-oxide; T2DM, type 2 diabetes mellitus; NAFLD, non-alcoholic fatty liver disease; AS, atherosclerosis; RA, rheumatoid arthritis; CRC, colorectal cancer; OSCC, oral squamous cell carcinoma; PD, Parkinson's disease; SLE, systemic lupus erythematosus; T1DM, type 1 diabetes mellitus; IL, interleukin; Th17, T helper 17 cell; Treg, regulatory T cell. The schematic outline of the image was created using Doubao AI (ByteDance).

gut, depleting beneficial bacteria (*Bifidobacterium* and *Faecalibacterium*), enriching *Escherichia coli-Shigella*, lowering ZO1/occludin, raising epithelial apoptosis and fueling a flora-metabolism-inflammation loop (48,49). *Porphyromonas gingivalis* (Pg) reduces gut microbial α-diversity, expands intestinal IL-9^{+}CD4^{+} T cells and represses tight junction genes to disrupt barrier integrity (50). Interventions include indigo (via flora-butyrate-Th17/Treg axis) (51), *Lactobacillus acidophilus* plus Huan Kui Le suspension (52), bile acid-farnesoid X receptor (FXR)/G protein-coupled bile acid receptor 5 modulation (53) and nutrient correction (methionine/tryptophan/niacin) (54). Periodontitis and IBD form a bidirectional oral-gut loop; Pg, Fn and other oral pathogens drive Th17-mediated intestinal inflammation via the 'multiple-hit' pathway (55,56). Pg worsens colitis by suppressing linoleic acid (LA)-AhR signaling, unbalancing Th17/Treg, which LA supplementation reverses (57). *Lactobacillus* R0052 (58), arctigenin (44) and cichoric acid (59) also repair barrier, flora and immune balance in IBD. The oral-gut axis is a central initiator and amplifier in IBD pathogenesis; stratified barrier-immune-metabolic targeting will markedly improve long-term remission rates.

Chronic periodontitis. It induces intestinal barrier damage and bacterial translocation via the oral-gut axis, forming a bidirectional inflammatory loop. Periodontitis alters mouse intestinal β diversity, increases the *Firmicutes*/*Bacteroidetes* ratio, reduces *Akkermansia* and butyrate-producing *Eubacterium* and impairs barrier structure (60,61). Patients show persistent oral-gut microbial imbalance; periodontal treatment improves oral flora but rarely reverses intestinal disorders (62). Grade C periodontitis presents elevated salivary *Fusobacteriota* and abnormal intestinal flora ratio; non-surgical periodontal therapy improves both flora and reduces systemic inflammation (63). Periodontal treatment combined with metformin mitigates bone loss in obese patients via the oral-gut-bone axis (47) and periodontal dysbiosis induces liver lipid toxicity through the oral-gut-liver axis (64). New evidence indicates periodontitis is driven by oral-gut metabolic, microbial and signaling imbalances (13) and it exacerbates ulcerative colitis (UC) by disrupting flora and tight junctions (65). Periodontitis remotely disturbs systemic homeostasis via the oral-gut axis, requiring combined oral-intestinal intervention for optimal control.

Long COVID. Long COVID is accompanied by metabolic and immune dysregulation, with intestinal barrier disruption and oral-gut bacterial translocation as core pathological features (66). Similar to other barrier-dominant diseases, long COVID may involve oral-gut microbial dysbiosis, elevated intestinal permeability and LPS translocation, which requires further validation in large cohort studies. Severe COVID-19 patients receiving extracorporeal membrane oxygenation present marked oral-gut axis imbalance, including poor oral health (high Oral Assessment Guide Fukuoka University Hospital score) (67), intestinal dysfunction (high Bristol Stool Form Scale score) and immune disturbance (high

neutrophil-to-lymphocyte ratio), forming a vicious cycle of oral impairment-intestinal-dysbiosis-immune injury that is directly associated with mortality (67). The COVID-19 virus can also damage the intestinal barrier via superantigen motifs, increase permeability and trigger multisystem inflammatory syndrome in children and long COVID through sustained viral antigen translocation (68). The oral-gut axis is a key pathological node in long COVID; targeted barrier repair and microbial regulation may help break the vicious cycle and improve prognosis.

Alcoholic liver injury. Alcoholic liver injury is identified as a novel barrier-dominant disease. Oral Pg translocates to the intestine, elevates *Proteobacteria* and *Escherichia coli/Shigella*, depletes *Akkermansia*, downregulates the tight junction protein ZO-1, reduces goblet cell count, increases intestinal permeability and promotes LPS entry into the circulation. This activates the TLR4/NF-κB pathway, triggers systemic inflammation and aggravates alcoholic fatty liver, hepatic inflammation and fibrosis (69). Oral pathogenic bacterial translocation is a critical hidden driver of alcoholic liver injury; early oral-gut barrier protection can effectively mitigate liver damage progression.

Chronic apical periodontitis (*CAP*). CAP is classified as a new barrier-dominant disease. Fn derived from apical infection enters the bloodstream, colonizes the intestine at 2 weeks and the kidney at 8 weeks, induces sustained reduction in *Verrucomicrobia* (*Akkermansia*), increases *Proteobacteria* at 2 weeks and raises the *Firmicutes*/*Bacteroidetes* ratio at 8 weeks, impairing intestinal mucosal anti-inflammatory and defensive functions (70). CAP also reshapes gut microbiota via the oral-gut axis, enriches *Lachnospiraceae* and *Ruminococcaceae* and promotes AS through the TMAO metabolic pathway (71). Chronic apical periodontitis acts as a silent systemic risk source via the oral-gut axis; timely root canal therapy and microbiota modulation are essential to prevent distant organ injury.

Metabolism-dominant diseases. Biomarker criteria: fecal butyrate <7.8 μmol/g, TMAO >10 μmol/l, reduced SCFA production, abnormal bile acid metabolism, disturbed amino acid and lipid metabolism.

T2DM. Insulin resistance is driven by oral-gut microbial translocation and disturbed glycine betaine metabolism (72). T2DM patients show an elevated *Firmicutes*/*Bacteroidota* ratio, enriched *Lachnospiraceae* and *Faecalibaculum* and abnormal glucose-lipid metabolism (73). Long-term T2DM reduces beneficial bacteria and fecal tryptophan derivatives, activating the retinoic acid-inducible gene I-like receptor pathway and triggering chronic intestinal and systemic inflammation (74). Oral dysbiosis (enriched Pg, *Prevotella nigrescens* and *Treponema denticola*) is linked to higher salivary cadaverine and leucine, accelerating insulin resistance via the oral-gut axis (75). Interventions including termite mound polysaccharides, yeast β-glucan and Huoxue Jiangtang Decoction can reshape oral-gut flora, improve metabolism and alleviate insulin resistance (76-78). Ethnic differences exist in oral-gut flora profiles between Dai and Han patients (79). New evidence confirms that gut dysbiosis reduces SCFA and glucagon-like peptide-1 (GLP-1) secretion; probiotic yogurt improves glycemic and lipid profiles (80), while high-sugar/high-fat diets disrupt oral-gut flora and promote T2DM progression. The oral-gut axis is a core metabolic hub in T2DM; personalized flora-targeted interventions can effectively improve insulin resistance and systemic metabolic disorders.

Hypertension. Hypertension belongs to the oral-gut microbial transmission subtype, marked by reduced SCFA-producing bacteria and activated inflammatory metabolic pathways (81). Elderly hypertensive patients present higher *Klebsiella* and *Streptococcus*, while long-lived hypertensive individuals maintain abundant SCFA producers and efficient acetate absorption to alleviate target organ damage (82). Probiotic fermented milk, curcumin, losartan and early neonatal flora intervention can regulate gut microbiota, boost SCFA production, repair intestinal barrier and reduce blood pressure or vascular inflammation (83,84). Recent evidence confirms hypertension involves gut flora-SCFA-vascular tone imbalance and impaired SCFA signaling (85); TMAO shows a dose-dependent association with hypertension risk (18) and high-amylose maize starch-based (HAMSAB) prebiotics increase SCFA to markedly lower systolic blood pressure (85). The oral-gut axis serves as a key regulatory node in hypertension; SCFA enhancement and flora remodeling offer promising adjunctive strategies for blood pressure management.

NAFLD. Intestinal-liver axis imbalance, reduced SCFA synthesis and disrupted bile acid metabolism drive hepatic steatosis (86). NAFLD patients present oral flora disturbance and elevated LPS/lactoferrin; 12-week exercise improves oral microbial diversity and lowers systemic inflammation (87). Periodontitis exacerbates liver fibrosis via the oral-gut-liver axis by enriching oral pathogens, activating hepatic NF-κB and increasing inflammatory immune cells (88). Gubra Amylin NASH (GAN) diet-induced oral-gut axis disorder triggers intestinal leakage and liver steatosis through abnormal bile acid and fatty acid metabolism (89). Lentinan and pasteurized wheat starch alleviate NAFLD by repairing the intestinal-liver axis, reshaping gut flora, lowering oxidative stress and inhibiting LPS-TLR4-NF-κB signaling (86,90). The oral-gut-liver axis is a core pathological pathway in NAFLD; combined oral flora regulation and intestinal barrier repair can effectively improve liver steatosis and fibrosis.

Obesity. Obesity has been added as a new metabolism-dominant disease. A high-fat diet elevates the *Firmicutes*/*Bacteroidetes* ratio, depletes beneficial bacteria, increases intestinal permeability and triggers systemic low-grade inflammation via the LPS-TLR4/NF-κB pathway (91). Blueberry anthocyanins reverse flora dysbiosis, enhance SCFA and improve obesity and lipid metabolism (92). Obesity is closely linked to oral microbial imbalance; obese individuals with acanthosis nigricans show distinct oral flora changes that promote disease progression (93). Caloric restriction followed by high-fat refeeding, as well as severe obesity, both disrupt gut and oral flora structure and metabolism (94,95). A novel synbiotic formulation ameliorates obesity by regulating the flora-fat axis and repairing intestinal barrier (91). New evidence indicates high-sugar/high-fat diets disturb SCFA and methane metabolism, while arctigenin improves obesity by reshaping gut flora and boosting SCFA production (44,96). The oral-gut axis plays a vital role in obesity development; targeted microbial and metabolic regulation offers an effective new approach for obesity control.

Post-cholecystectomy complications. Post-cholecystectomy complications are newly classified as a metabolism-dominant disease. Cholecystectomy disrupts intestinal microbial homeostasis and metabolic profiles, increasing *Bacteroidetes*, decreasing *Ruminococcaceae* and *Faecalibacterium* and enriching *Escherichia coli* and *Prevotella*. It also disturbs bile acid enterohepatic circulation, reduces fecal SCFA and elevates intestinal calprotectin, thereby raising risks of postoperative syndrome, NAFLD, CRC and cardiovascular diseases (97). Intestinal flora and metabolic disturbance are core pathological bases of post-cholecystectomy complications; targeted SCFA and bile acid regulation can effectively reduce postoperative risks.

Postmenopausal metabolic syndrome. Postmenopausal metabolic syndrome is added as a new metabolism-dominant disease. Ovariectomized mice show reduced intestinal flora α-diversity, enriched pro-inflammatory bacteria and depleted beneficial bacteria, accompanied by insulin resistance, abnormal lipid synthesis and elevated hepatic and macrophage pro-inflammatory factors. Fish oil combined with hyperthermia can alleviate these metabolic abnormalities by regulating intestinal flora (98). Intestinal microecological imbalance drives postmenopausal metabolic disorders; flora-modulating interventions provide a new strategy for managing menopausal metabolic syndrome.

AS. AS is newly defined as a metabolism-dominant disease. AS is linked to intestinal flora-choline-TMAO metabolic imbalance, where overactivated choline trimethylamine-lyase (CutC) enzyme increases trimethylamine (TMA) and subsequent hepatic TMAO production, promoting plaque formation (99). Enriched TMA-producing bacteria trigger inflammation, platelet hyperreactivity and impaired reverse cholesterol transport (99). Berberine blocks the TMAO pathway to lower TMAO and reduce plaque burden (99). Periodontitis and CAP also reshape gut flora, raise serum TMAO and promote AS (71). The flora-TMAO axis is a key therapeutic target for AS; combined oral-gut flora regulation can effectively inhibit plaque progression.

Epilepsy. Epilepsy is added as a new metabolism-dominant disease. A one-month classic ketogenic diet (KD) reduces total SCFA by 55%, acetate by 64%, propionate by 33% and butyrate by 20% in epilepsy patients (100). The extremely low carbohydrate and fiber content in KD limits substrates for SCFA-producing bacteria, which is the main cause of SCFA reduction (100). Long-term SCFA deficiency may impair intestinal barrier and increase risks of intestinal inflammation and tumors (100). KD-induced SCFA deficiency is a hidden risk in epilepsy management; supplementary SCFA or prebiotics can help maintain intestinal homeostasis during ketogenic therapy.

Immunity-dominant diseases. Biomarker criteria: elevated IL-17A, increased Th17/Treg ratio, activated TLR4/NF-κB, abnormal activation of NLRP3 inflammasome and disturbance of mucosal immune function.

RA. RA is driven by intestinal-joint axis immune imbalance, Th17/Treg disturbance and excessive pro-inflammatory cytokine release (101). The oral mucosa is an early initiation site for RA autoimmunity; Pg promotes citrullination via peptidylarginine deiminase (PAD) enzymes and triggers systemic immune dysregulation (102). The high-virulence porphyromonas gingivalis peptidylarginine deiminase T2 variant subtype alters salivary flora and partially explains the female predominance of RA (103). Early RA patients display abnormal oral flora diversity and metabolic dysfunction independent of periodontitis (104). RA involves bidirectional oral-gut microbial imbalance, with reduced intestinal SCFA producers and elevated pro-inflammatory taxa; periodontal therapy plus methotrexate synergistically corrects this disorder (105). Genetic polymorphisms such as TAS2R38 also modify oral flora and RA risk (106). Gut flora-Th17 immune imbalance in RA; *Bifidobacterium longum* RAPO, oral-gut barrier repair and traditional herbal medicine all alleviate inflammation by restoring flora and Th17/Treg balance (101,107,108). The oral-gut axis is a core upstream driver of RA autoimmunity and inflammation; integrated oral microbial control and immune-flora regulation can markedly improve RA intervention outcomes.

CRC. CRC is driven by oral pathogenic bacteria colonization, intestinal immune microenvironment disorder and oncogenic pathway activation (109). CRC patients show reduced butyrate-producing bacteria, enriched Fn and *Bacteroides fragilis* and elevated intestinal leakage marker zonulin (110). Oral Fn suppresses anti-tumor immunity via the Fap2-TIGIT pathway, impairing immune surveillance (110). Periodontitis accelerates CRC through the oral-gut-tumor axis by upregulating pro-carcinogenic metabolites and activating inflammatory pathways (111). Oral pathogenic bacteria are enriched in the intestine of CRC patients and a combined bacteria-metabolite model achieves high diagnostic accuracy (112,113). CRC treatment response is closely linked to oral-gut flora status; Fn predicts chemotherapy resistance and poor prognosis (71,110). Salivary flora serves as a non-invasive screening tool with high predictive power (114). Fecal microbiota transplantation (FMT) combined with immunotherapy reverses microsatellite stable (MSS)-CRC drug resistance (115) and oral bacterial translocation directly raises CRC risk (116). The oral-gut-tumor axis is a key driver of CRC initiation and progression; targeted oral-gut flora regulation can improve early screening, treatment sensitivity and long-term prognosis.

Oral squamous cell carcinoma (OSCC). OSCC is characterized by enrichment of oral carcinogenic bacteria, impaired local immune tolerance and abnormal apoptotic regulation (117). OSCC lesions show markedly lower bacterial α-diversity with altered pathogenic and beneficial flora composition (118). Pg-dominant periodontal flora promotes OSCC proliferation by activating the IL-17/signal transducer and activator of transcription 3 (STAT3) pathway and recruiting tumor-associated macrophages (119). Betel quid chewing drives progressive oral flora imbalance from precancerous lesions to OSCC (120); Fn is a reliable diagnostic marker for OSCC (121). Periodontitis promotes OSCC via the γδ T-IL17-oral-gut flora axis and disturbed purine metabolism (122); *Candida albicans* overgrowth disrupts intestinal flora and impairs immunotherapy efficacy (123). Outer membrane vesicles (OMVs) from Pg and Fn mediate OSCC progression and induce distal organ damage (124). The oral-gut axis plays a critical role in OSCC development and metastasis; early regulation of oral microecology and targeted

inhibition of pathogenic bacteria can effectively prevent tumor progression and improve treatment response.

Oropharyngeal cancer. Oropharyngeal cancer is added as a new immunity-dominant disease. Pg, *Fusobacterium* and *Prevotella* are associated with elevated cancer risk; oral *Streptococcus* maintains immune homeostasis via TLR2-mediated regulation of $Foxp3^+$ Tregs and global oral flora structure shows stronger predictive value than single species (125). Patients display increased *Fusobacteriota* and *Actinobacteriota*, while healthy oral cavities are dominated by *Firmicutes* (*Streptococcus*); oral pathogenic bacteria can translocate to the gut and raise the risk of gastrointestinal malignancies (125). Recent evidence indicates oral *Streptococcus* (GAS) triggers aberrant immunity via molecular mimicry, promoting autoimmunity and increasing oropharyngeal cancer risk (108). Oral immune-microbial imbalance is a key initiator of oropharyngeal carcinogenesis; early oral microecological regulation can reduce cancer susceptibility.

Systemic lupus erythematosus (SLE) complicated with hypertension. SLE with hypertension is newly classified as an immunity-dominant disease. TLR7-driven lupus autoimmunity induces hypertension and vascular dysfunction through gut dysbiosis, characterized by reduced *Sutterella* and *Anaerovibrio*, elevated *Actinobacteriota*, disrupted *Firmicutes*/*Bacteroidetes* ratio, impaired intestinal barrier, bacterial translocation, oxidative stress and activated Th17/IL-17a signaling in mesenteric lymph nodes and aorta (126). FMT confirms that imbalanced flora can directly transfer the hypertensive phenotype (126). Gut immune-microbial disturbance bridges SLE and hypertension; targeted flora modulation can alleviate vascular inflammation and control blood pressure.

Immunosuppression. Immunosuppression is added as a new immunity-dominant disease. *Holothuria leucospilota* polysaccharide (HLP) repairs intestinal flora-immune imbalance in immunosuppressed mice by increasing *Lactobacillus* and *Bacteroides*, decreasing *Staphylococcus* and *Faecalibacterium*, enhancing SCFA production, activating TLR2/4 and NF-κB pathways and restoring immunoglobulin and cytokine levels (127). New evidence shows compound probiotics temporarily reduce intestinal colonization of multidrug-resistant Gram-negative bacteria in elderly patients and lower nosocomial infection risk (127). Intestinal flora-immune crosstalk is critical for immune recovery; flora-enhancing interventions effectively improve immune function in immunosuppressed individuals.

Pulmonary hypertension (PH). PH is newly defined as an immunity-dominant disease. PH involves dynamic intestinal flora-metabolic disorders, with increased *Firmicutes*, decreased *Bacteroidetes* and abnormal metabolism of histidine, alanine, serine and asymmetric dimethylarginine (ADMA) (128,129). *Lactobacillus rhamnosus* Probio-M9 improves PH via the gut-lung axis by normalizing flora, correcting SCFA and nitric oxide metabolism and reducing pulmonary vascular remodeling (128,129). The gut-lung axis is a key regulatory target in PH; gut flora-metabolic modulation can alleviate vascular remodeling and improve cardiopulmonary function.

Parkinson's disease (PD). PD is added as a new immunity-dominant disease. PD patients with dysphagia show severe oral soft-tissue flora abnormalities, with enrichment of *Streptococcus pneumoniae*, *Mycoplasma orale* and *Prevotella intermedia*; dysphagia, hypersalivation and low salivary pH drive dysbiosis (130). Oral pathogens translocate to the gut via swallowing, disrupt distal microecology, raise aspiration pneumonia risk and exacerbate neuroinflammation via the oral-gut-brain axis (130). Gut tryptophan metabolite melatonin imbalance contributes to PD neuroinflammation (131). Oral-gut-brain axis disturbance accelerates PD progression; oral care and flora regulation can reduce complications and slow disease deterioration.

Hematopoietic stem cell transplantation (HSCT)-related ulcerative mucositis. HSCT-related ulcerative mucositis is newly classified as an immunity-dominant disease. Patients show elevated *Mycoplasma salivarium* in saliva and depleted symbionts including *Rothia* and *Anaerobacter*; post-transplant intestinal α diversity declines, *Enterococcus* surges and *Bacteroides fragilis* drops (132). Oral-intestinal flora imbalance is closely associated with the onset and severity of mucositis (132). Oral-gut flora disruption is a core trigger of transplant-related mucositis; peri-transplant flora protection can reduce mucosal injury and complications.

T1DM. T1DM is added as a new immunity-dominant disease. T1DM involves bidirectional oral-gut flora imbalance: salivary diversity decreases, *Streptococcus*, *Actinomyces* and *Rothia* increase, while *Prevotella* and *Veillonella* decrease (16). High-sugar saliva promotes acid-producing bacteria overgrowth; the gut shows reduced SCFA producers, elevated *Bacteroides*, barrier damage and increased zonulin (16). Oral bacteria translocate to the gut, trigger autoimmunity and destroy pancreatic β cells; salivary flora can serve as an early non-invasive marker and periodontitis worsens glycemic control (16). Oral-gut immune-microbial dysregulation initiates T1DM; early oral-gut flora intervention may delay or prevent β-cell damage.

Osteoporosis. Osteoporosis is newly defined as an immunity-dominant disease. Osteoporotic mice exhibit reduced intestinal *Allobaculum* and *Parasutterella*, increased *Akkermansia*, disturbed tryptophan metabolism and decreased melatonin (131). SCFA declines, TMAO rises, M1 macrophages predominate, pro-inflammatory factors increase and intestinal barrier integrity is lost (131). Melatonin supplementation reverses flora imbalance, elevates SCFA, lowers TMAO, balances macrophage polarization and improves bone density (131). The gut-immune-bone axis regulates bone homeostasis; flora-metabolic modulation provides a novel strategy for osteoporosis prevention and treatment.

Overlap subtypes involve concurrent abnormalities in two or more biomarker panels, often occurring in advanced chronic diseases. Diabetic periodontitis presents combined barrier-metabolism-immunity imbalance, with oxidative stress and gut dysbiosis forming a vicious cycle that aggravates inflammation and bone loss; curcumin and FMT can break this cycle (133) and gut flora regulates α-tocopherol acetate via the STAT3 pathway to alleviate alveolar bone destruction (134). Periodontitis with AS involves triple-axis imbalance, reshaping gut flora, elevating TMAO, triggering systemic inflammation and promoting plaque formation (71,135). Periodontitis with liver fibrosis allows oral pathogens to translocate to the liver, activate NF-κB and worsen fibrosis (88). Early pregnancy periodontitis disturbs oral-gut flora and metabolism, increasing

Table IV. Stratified three-dimensional combinatorial intervention strategy.

Subtype	Core intervention regimen	Target pathways
Barrier subtype	Barrier repair + remove oral-derived pathogens + microbiota remodeling	Tight junction (ZO-1/Occludin), LPS translocation
Metabolism subtype	SCFA supplementation + TMAO inhibition + dietary fiber intervention	SCFA-GPR, TMAO-CutC/FMO
Immunity subtype	Anti-IL-17/STAT3 + Th17/Treg balance + local oral therapy	TLR4/NF-κB, Th17/Treg, IL-17 signaling
Overlap subtype	Multi-dimensional combinatorial therapy	Barrier + metabolism + immunity crosstalk

SCFA, short-chain fatty acid; TMAO, trimethylamine N-oxide; IL-17, interleukin-17; STAT3, signal transducer and activator of transcription 3; TLR4, Toll-like receptor 4; NF-κB, nuclear factor κB; Th17/Treg, T helper 17/regulatory T cells; GPR, G protein-coupled receptor; CutC, choline trimethylamine-lyase; FMO, flavin-containing monooxygenase.

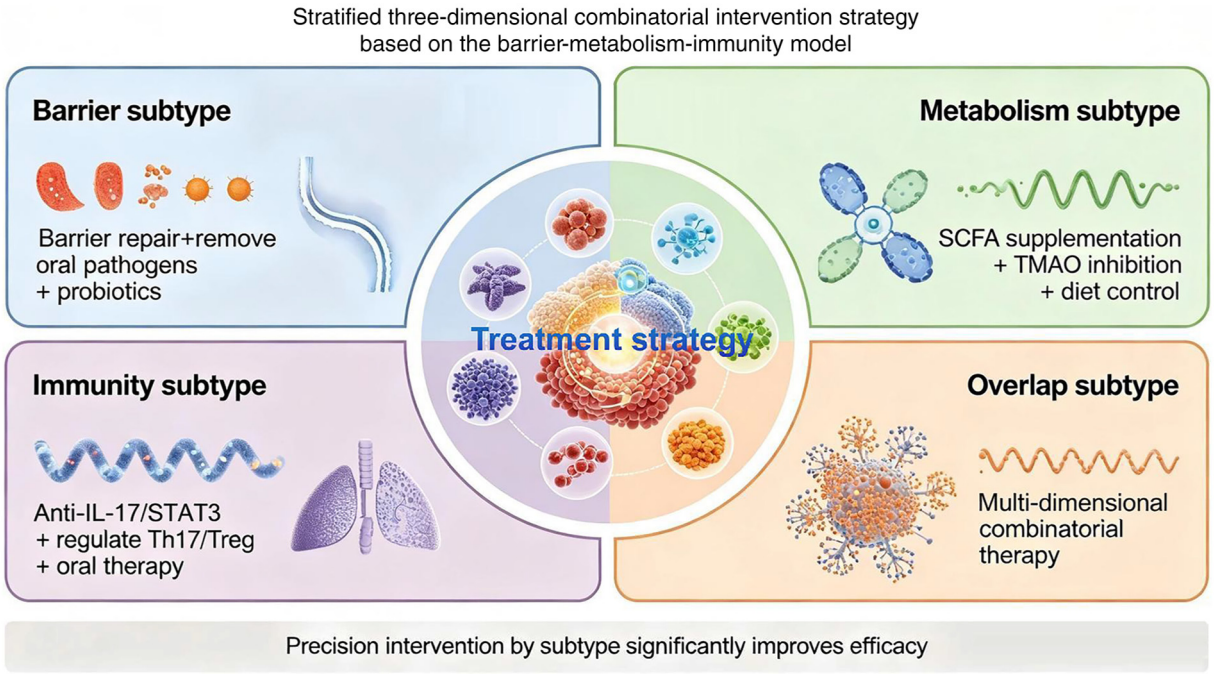

Figure 5. Stratified three-dimensional combinatorial intervention strategy. Precision intervention framework tailored to the three subtypes of oral-gut axis imbalance. Barrier-dominant diseases: Prioritize barrier repair, targeted elimination of oral-derived pathogens and probiotic supplementation. Metabolism-dominant diseases: Focus on SCFA replenishment, TMAO inhibition and dietary control. Immunity-dominant diseases: Use immune-targeted therapy (such as anti-IL-17/STAT3, Th17/Treg balancing) combined with oral intervention. Overlap subtypes: require multidimensional combinatorial therapy targeting barrier, metabolic and immune pathways simultaneously to break progressive pathological cycles. SCFA, short-chain fatty acid; TMAO, trimethylamine N-oxide; IL STAT3, signal transducer and activator of transcription 3; IL, interleukin. The schematic outline of the image was created using Doubao AI (ByteDance).

risks of glycemic dysregulation, dyslipidemia and adverse pregnancy outcomes; the *Coprococcus* + triglyceride + L-urobilin panel effectively assesses such imbalance (136). Overlap subtypes reflect severe multi-dimensional disorders of the oral-gut axis; comprehensive combinatorial intervention targeting barrier, metabolism and immunity is essential to break progressive pathological cycles.

4. Clinical translation and therapeutic strategies

As shown in Table IV, given the critical roles of microbial homeostasis in the barrier-metabolism-immunity three-dimensional regulatory network, targeted modulation of the oral-gut microbiota has become the most direct and foundational strategy for clinical intervention (Fig. 5).

Microbiota modulation. Probiotics, postbiotics, prebiotics, synbiotics and FMT restore microbial balance. Heat-inactivated lactobacilli improve mucosal and intestinal barrier function (137,138) and optimized FMT alleviates colitis-related dysbiosis (139). Targeted interventions include *Lactobacillus acidophilus* with Chinese medicine for UC (52), Probio-M9 for PH via the gut-lung axis (129), indigo for regulating the butyrate-Th17/Treg pathway (51), yeast β-glucan for

the gut-liver axis (77), HLP for immunosuppression (127), heat-inactivated *Lactobacillus paracasei* GMNL-346 against OSCC (140) and synbiotics for obesity (91). Evidence shows that FMT achieves durable remission in recurrent UC (141); donor screening improves safety (142); phage/nanodrugs targeting Fn block the oral-gut-tumor axis (108); probiotic yogurt and compound probiotics improve T2DM and reduce drug-resistant bacteria (80,127). Targeted microbiota-based interventions effectively restore oral-gut axis homeostasis and represent a promising strategy for systemic disease prevention and treatment.

Metabolic-targeted therapies. Metabolic-targeted therapies mainly include SCFA supplementation, TMAO inhibition, bile acid adjustment and dietary fiber intervention. Targeted regulation of tryptophan metabolism and TMAO synthesis improves cardiovascular and metabolic diseases (143) and SCFA replenishment alleviates intestinal metabolic disorder and systemic inflammation (144). SCFA mixtures suppress CRC cell proliferation, with butyrate playing a major role (110); bile acid regulation enhances colitis treatment efficacy (53); *Akkermansia* and *Bifidobacterium* prevent NAFLD via the FXR-gut flora axis (145); dietary fiber improves lupus cardiovascular complications (146); termite mound polysaccharides, lentinan and pasteurized wheat starch regulate the gut-liver axis to relieve metabolic disorders (76,86,90). New evidence shows berberine reduces TMAO and atherosclerotic plaques by inhibiting CutC/flavin-containing monooxygenase (FMO) (99); HAMSAB prebiotics elevate SCFA and improve hypertension (85); LA supplementation reverses Pg-induced colitis (57); melatonin ameliorates osteoporosis via the flora-SCFA-TMAO axis (131); ketogenic diets require prebiotics/probiotics to avoid SCFA reduction and intestinal injury (100). Precise regulation of the flora-metabolite axis is a core strategy for metabolic and inflammatory diseases; multi-metabolite combined intervention can effectively maintain oral-gut axis homeostasis and improve systemic outcomes.

Immune modulation. Immune modulation focuses on correcting Th17/Treg balance, TLR4/NF-κB and immune cell migration. Blocking TLR4/NF-κB and NLRP3 pathways mitigates systemic inflammation (147), while balancing Th17/Treg alleviates autoimmune diseases (148). Oat alkaloid C, thymol and peroxisome proliferator-activated receptor agonists relieve colitis by regulating flora and barrier function (149-151); electroacupuncture reduces periodontal bone loss (152); inhibiting IL-17/STAT3 suppresses OSCC and RA progression (104,122); chlorhexidine improves oral dysbiosis and protects the intestinal barrier (63). Blocking Fap2-TIGIT enhances CRC immunotherapy (108); neutralizing IL-17A improves OSCC treatment by balancing oral fungi-bacteria interactions (123). Immune crosstalk is a key effector node of the oral-gut axis; precise immune-targeted regulation can effectively block systemic inflammation and improve disease outcomes.

Local oral intervention. Local oral interventions include periodontal therapy, chlorhexidine, probiotic mouthwash and oral barrier repair. Basic periodontal treatment blocks oral-gut microbial translocation and lowers systemic inflammation (60), while oral probiotics improve local dysbiosis (137). Periodontal treatment repairs intestinal flora and barrier in hyperlipidemia (61); root canal therapy stops systemic spread of oral pathogens (70); Nell-1 plus gold nanoparticles regulate periodontal inflammation (153); inhibiting Pg PPAD reduces RA risk (103); oral care reduces carcinogenic bacteria and lowers OSCC/CRC risk (71,118); combined periodontal and metformin therapy ameliorates bone loss in obese periodontitis (47). Oral care improves severe COVID-19 prognosis (67); targeting oral pathogens reduces T1DM and RA risk (16,108); salivary flora screening enables early disease warning (16,114). Local oral intervention is the first line to protect the oral-gut axis; standardized oral management can effectively prevent systemic diseases and improve clinical prognosis.

Stratified three-dimensional combined intervention. Based on the subtype classification and core pathological mechanisms identified aforementioned, the present review proposed a stratified three-dimensional combined intervention strategy that targets the dominant disordered module while integrating synergistic regulation of the other two modules. This personalized, stepwise approach markedly enhances therapeutic efficacy by addressing the root cause rather than just symptoms (Fig. 6).

Barrier-dominant. Barrier repair + microbiota remodeling (154); for IBD and alcoholic liver injury, barrier repair combined with targeted removal of oral pathogenic bacteria and beneficial microbiota supplementation markedly boosts therapeutic effects (49,69). For CAP, root canal therapy plus *Akkermansia* supplementation blocks oral-gut axis damage and restores intestinal barrier (70). For periodontitis, non-surgical periodontal treatment with intestinal probiotics repairs gut flora and barrier function (61). For IBD, combined periodontal care, FMT and LA supplementation interrupts the multi-hit pathogenic cascade and improves outcomes (57,154). For CAP, root canal therapy with probiotics prevents secondary intestinal and cardiovascular injuries (70,71). Sequential barrier repair and precise oral-gut microbiota modulation form a synergistic strategy that effectively blocks pathological signaling and improves prognosis in barrier-dominant diseases.

Metabolism-dominant. Metabolite regulation + dietary control (155); for T2DM and NAFLD, dietary intervention plus metabolite regulation (SCFA supplementation, TMAO inhibition) enhances metabolic improvement (82,87). For hypertension, curcumin extract and probiotic fermented milk optimize gut flora and metabolic pathways (84,155). For obesity, synbiotics combined with a low-fat diet reshape flora, alleviate inflammation and ameliorate obesity (91). For post-cholecystectomy patients, probiotics plus a low-fat, high-fiber diet maintain flora stability and lower complication risk (97). For postmenopausal metabolic syndrome, fish oil combined with hyperthermia regulates flora and corrects metabolic disorders (98). For AS, berberine plus reduced red meat intake inhibits the TMAO pathway and mitigates plaque formation (99). For epilepsy patients on a ketogenic diet, prebiotics/probiotics replenish SCFA and protect intestinal integrity (100). For osteoporosis, melatonin plus probiotics modulate the gut flora-SCFA-TMAO axis to increase bone density (131). Personalized combined intervention targeting

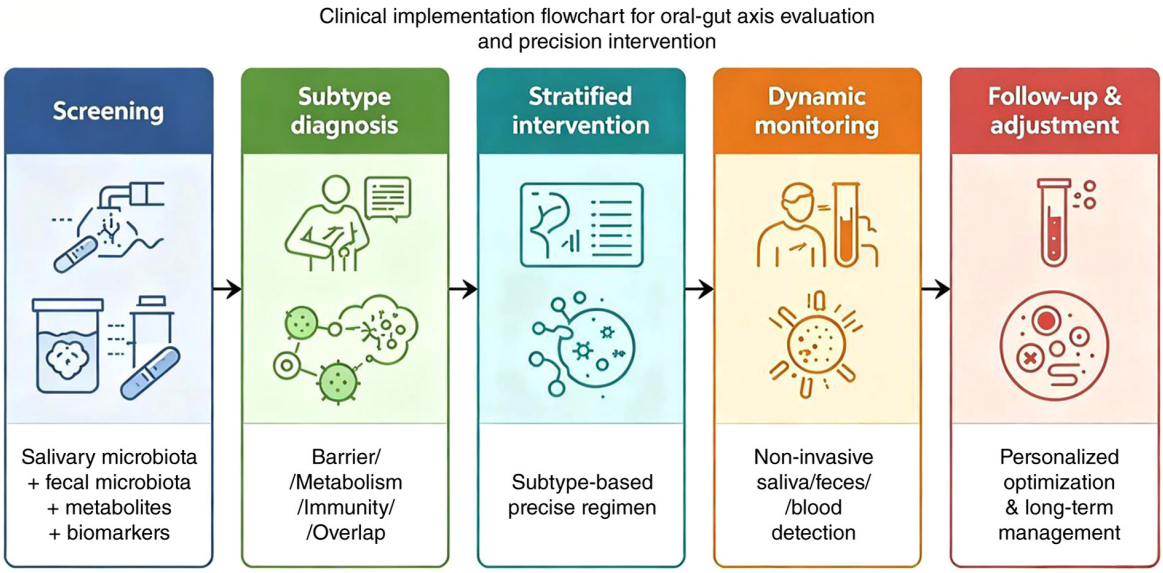

Figure 6. Clinical implementation flowchart for oral-gut axis evaluation and stratified precision intervention. Clinical workflow for translating the three-dimensional regulatory model into practice. Patients undergo initial screening using saliva and fecal microbiota plus metabolite detection. Individuals are then stratified into barrier-dominant, metabolism-dominant, immunity-dominant, or overlap subtypes. Targeted intervention is administered according to subtype classification. Non-invasive dynamic monitoring (saliva, feces and blood) is performed longitudinally to assess microbial translocation, barrier function, metabolite levels and immune status. Intervention regimens are adjusted iteratively to achieve sustained remission and improve long-term prognosis. The schematic outline of the image was created using Doubao AI (ByteDance).

metabolism and flora is highly effective for metabolism-dominant diseases, offering a reliable approach to improve systemic metabolic homeostasis.

Immunity-dominant. Immune targeting + oral intervention (157). For RA and OSCC, immune targeting (inhibiting IL-17/STAT3, balancing Th17/Treg) combined with periodontal therapy and oral probiotics blocks oral flora-driven upstream pathogenesis and enhances efficacy (104,119). For CRC, clearing oral pathogenic bacteria plus SCFA supplementation strengthens immune surveillance and suppresses tumor progression (110,111). For SLE-associated hypertension, regulating gut flora and inhibiting the Th17/IL-17 axis improves vascular function (126). For PD, enhanced oral care with probiotics lowers aspiration pneumonia risk and slows disease progression (130). For immunosuppressed patients, HLP plus probiotics repairs gut flora and restores immunity (127). For T1DM, oral care combined with probiotics blocks oral-gut autoimmune signaling and delays onset (16). For CRC, FMT plus immunotherapy reverses drug resistance (115); for OSCC, antifungal treatment plus oral cleaning boosts immunotherapy outcomes (123). Combined immune-targeted and oral-gut flora intervention serves as a core strategy for immunity-dominant diseases, effectively breaking immune dysregulation and improving clinical responses.

Overlap subtypes. Multi-dimensional combinatorial therapy (158). For diabetic periodontitis, antioxidant therapy (curcumin) combined with probiotic intervention and periodontal treatment can break the vicious cycle between oxidative stress and microbial dysbiosis, thereby improving periodontal conditions and metabolic status (133). For periodontitis accompanied by AS, root canal therapy combined with targeted regulation of *Akkermansia* and lipid-lowering treatment can block the pathological signaling of the oral-gut-cardiovascular axis (135,159). For periodontitis complicated with liver fibrosis, periodontal treatment combined with probiotics and hepatoprotective therapy can block the oral-gut-liver axis and alleviate hepatic injury (88). For OSCC, antifungal therapy, probiotic intervention and oral hygiene care can collectively restore oral-gut microbial balance and enhance the efficacy of immunotherapy (123). Overlap subtypes require multi-dimensional combinatorial interventions targeting barrier, metabolism and immunity; such integrated strategies can effectively disrupt progressive pathological cycles and improve the prognosis of complex comorbidities.

5. Challenges and future perspectives

Although the oral-gut axis has been increasingly recognized as a key regulatory network linking oral health to systemic homeostasis, its clinical translation remains constrained by several critical limitations. These challenges span mechanistic validation, intervention consistency, real-time monitoring and overall study design, which collectively hinder the practical application of the three-dimensional barrier-metabolism-immunity model. Below are summarized the core obstacles and their underlying causes.

Core challenges

Insufficient causal evidence. Causal verification of the oral-gut axis remains difficult, as most current evidence is only correlative rather than definitive (66). Most studies are cross-sectional or based on animal experiments, lacking prospective human intervention cohorts and direct proof of oral-gut bacterial translocation; the molecular mechanisms of key pathogens such as Pg and Fn have not been fully elucidated (69,110). Numerous findings lack clinical translation and strain-level dynamic processes, disease-causing thresholds and non-bacterial microbes (fungi, viruses) remain

under-explored (123). Furthermore, a large number of studies ignore oral microbiome data and neglect upstream oral driving factors (141). Strengthening causal validation is essential to transform correlative observations into clinically actionable mechanisms.

High variability of intervention efficacy. Intervention efficacy varies widely due to baseline microbiota and host genetic background (148). Host genetics shapes oral flora composition and immune responses, with 27 oral bacterial taxa showing high heritability that affects treatment outcomes (160). Baseline flora structure also determines responses to interventions such as nitrate supplementation (161), while probiotic efficacy is limited by strain specificity, dosage and short duration (162). Ethnic differences, diet and lifestyle further modify flora and intervention generalizability (79,87). In addition, most probiotics fail to colonize the gut permanently (163) and long-term steroid use, radiotherapy and high-sugar/high-fat diets disrupt flora-metabolism-immunity homeostasis and weaken intervention stability (164,165). Personalized strategies based on baseline microbiota and host characteristics are needed to improve reliability.

Lack of real-time in vivo monitoring tools. Real-time *in vivo* monitoring tools for microbial translocation are lacking (166). The lack of unified microbial markers for various diseases (102,111); the lack of accurate detection methods for oral-gut bacterial translocation and real-time monitoring of flora dynamic changes (70,159); bacterial species-level resolution is insufficient (118,162). Detection methods are not unified across studies (111,162); non-invasive early screening tools are lacking (75,114). Developing standardized monitoring platforms is critical to enable precise evaluation and adjustment of interventions.

Other methodological and clinical limitations. Some studies are limited by small sample sizes, single-center designs and narrow population scope (94,118); most animal findings lack clinical translation (52,73); confounding factors including diet and lifestyle reduce accuracy (80); proton pump inhibitor (PPI) use, aging and hypertension promote oral-rectal translocation and increase confounding (116); radiotherapy, steroids and ketogenic diets independently disrupt the axis (164); surgical intestinal flora heterogeneity adds variability (167); and most FMT studies lack oral flora evaluation with safety blind spots (141,142). Emerging technologies such as organ-on-a-chip, clustered regularly interspaced short palindromic repeats (CRISPR), gnotobiotic models, multi-omics, single-cell sequencing, organoids and artificial intelligence (AI) enable precise causal verification and targeted intervention (89,112). Specific strains, metabolic pathways, immune nodes and nanodelivery systems provide measurable and editable targets for precision therapy (99). Rigorous, large-scale and controlled clinical designs are required to reduce bias and improve real-world applicability.

Future directions

Strengthening causal mechanistic exploration. Strengthen causal evidence using gnotobiotic models and gene editing (31). Clarify the mechanisms of oral-gut translocation and the roles of key strains (69,110); conduct multi-center prospective cohort studies (79,118). Verify oral-gut translocation at the strain level (such as Fn and *Streptococcus salivarius*) (116); validate critical metabolic axes including LA-AhR-Stat1 and tryptophan-indole (13,57); employ CRISPR editing to target the *tnaA*, *CutC* and *NLRP3* pathways (13); and clarify interactions among fungi, viruses and bacteria (16,123). High-quality causal evidence is the cornerstone of clinical translation; multi-model validation and multi-omics integration will help establish reliable mechanisms of the oral-gut axis.

Developing biomarker-driven precision intervention. Develop biomarker-based personalized intervention (168). It is necessary to construct flora-metabolite diagnostic models (112,113), perform early screening for high-risk populations (102), optimize the dosage and delivery mode of probiotics and prebiotics (140,162) and combine genetic testing to formulate precise intervention regimens (106,160). Metabolism-dominant diseases focus on SCFA supplementation, TMAO inhibition and scientific dietary regulation (96,99); overlap mixed subtypes require collaborative oral-intestinal combined treatment (10). Biomarker screening and subtype classification can markedly improve the individualization and effectiveness of oral-gut axis targeted therapy, providing new directions for standardized clinical prevention and treatment.

Building monitoring systems and expanding research boundaries. Establish non-invasive dynamic monitoring platforms (169). Saliva-based detection technology and unified diagnostic criteria should be developed to form standardized real-time monitoring systems (111,162). Integrated detection panels covering the oral-gut axis, SCFA metabolism and immune indicators help reflect holistic pathological changes. It is feasible to dynamically monitor CRC progression and oral pathogenic load, track microbial translocation induced by drugs and aging (116) and evaluate physical recovery after radiotherapy and surgery (167). In addition, portable detection devices can be optimized to meet the needs of clinical and household early screening (75,114).

Diversified oral-gut integrated intervention strategies should be explored comprehensively. Combined regimens including periodontal treatment, oral probiotics, intestinal regulation and natural medicine intervention can improve systemic inflammation (51). Perioperative oral care and anti-infection intervention help reduce axis disturbance (165). Supplementary intervention with SCFA and LA can alleviate metabolic and inflammatory diseases (57,85). FMT combined with immunotherapy provides a new direction for tumor treatment (108,115). Oral-intestinal dual-target preparations, nutrient regulation and targeted inhibition of key virulence factors also show broad application prospects (170).

The research scope of the oral-gut axis needs to be further expanded. More attention should be paid to its potential role in multiple systemic diseases (130), as well as the regulatory effects of lifestyle and external environment. In-depth exploration of multi-organ interactive networks and cross-axis crosstalk helps reveal systematic pathological mechanisms (130). Future research should also focus on early microbial colonization, epigenetic correlation and the interference of special diets and clinical drugs on flora homeostasis. In

summary, constructing standardized monitoring systems and optimizing combined intervention strategies, together with expanding multi-dimensional research boundaries, can greatly accelerate the clinical transformation of oral-gut axis theory and offer novel theoretical references for the comprehensive prevention and treatment of systemic diseases.

6. Conclusion

The oral-gut axis constitutes a dynamic bidirectional network governed by barrier integrity, metabolic signaling and immune crosstalk, whose disruption initiates and propagates a wide spectrum of systemic diseases. The present review established a unified barrier-metabolism-immunity three-dimensional regulatory model that redefines the core pathogenesis of oral-gut axis dysfunction, moving beyond traditional linear frameworks to emphasize cyclic interactions and causal stratification. Barrier damage serves as the initiating trigger enabling microbial translocation; metabolic disturbances act as signal amplifiers; and immune dysregulation functions as the final effector driving systemic inflammation. Together, these three modules drive disease progression via secondary interorgan axes including the liver, cardiovascular system, brain, joint, kidney and tumor-related pathways.

Clinical translation is advanced by subtype stratification into barrier-dominant, metabolism-dominant, immunity-dominant and overlap phenotypes, each with defined biomarkers and targeted intervention regimens. Stratified combinatorial therapy, including barrier repair, SCFA supplementation, TMAO inhibition, immune modulation and local oral care, markedly improves efficacy over single-target approaches. Despite remaining challenges in causal verification, individualized efficacy and real-time monitoring, emerging tools such as multi-omics, microbiota editing and non-invasive detection are accelerating clinical application.

In summary, this three-dimensional model provides a novel theoretical foundation and actionable clinical roadmap for precision diagnosis, stratified intervention and long-term management of oral-gut axis-related disorders. It bridges basic mechanistic research and clinical practice, highlighting the oral-gut axis as a promising target for preventing and treating complex systemic comorbidities. Future investigations focusing on causal mechanisms, biomarker panels and personalized combinatorial regimens will further unlock the clinical potential of this pivotal interorgan network.

Acknowledgements

Not applicable.

Funding

The present study was funded by Shanghai Administration of Traditional Chinese Medicine's 2025 Key Traditional Chinese Medicine Disease Construction Project (grant no. ZDBZ-202612), Research Project of Jiading District Health System (grant no. ZB202404), Research Project of Jiading District Health Commission (grant no. 2024-KY-ZD-04) and Hospital Level Talent Project of Nanxiang Hospital (grant no. 202415B).

Availability of data and materials

Not applicable.

Authors' contributions

MC, YY and QL were responsible for conceptualization, methodology, formal analysis, writing the original draft, writing, reviewing and editing. WL, XW and XL were responsible for data collection, formal analysis and writing the original draft. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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